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AUTHOR Parascandola, John
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ABSTRACT

Presented is a review of the development of the science of pharmacology, the study of the interaction of chemical agents with living matter. The origins of the field are traced from 17th century Europe to the present, with major emphasis upon the scientists and developments made in the field in the United States. (SL)

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The Early Development of Pharmacology in America

by John Parascandola
School of Pharmacy and
Department of History of Science
University of Wisconsin-Madison

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Although the word "pharmacology" has existed in the English language at least since the 17th century, the science of experimental pharmacology did not emerge as a distinct discipline until the 19th century. Originally, the term pharmacology seems to have been largely used either as a synonym for pharmacy (i.e., the art of compounding medicines) or, more usually, as a general term referring to the study of drugs. In this latter sense, it included the study of the origin, composition, physical and chemical properties, physiological effects, therapeutic uses and modes of preparation and administration of drugs, i.e., essentially all scientific knowledge concerning drugs. The term "materia medica" was also often used in this broad sense as essentially a synonym for pharmacology, although it sometimes had a more restricted meaning.

During the course of the 19th century, that portion of the science of drugs which concerned itself with the investigation of their physiological effects came to be called "pharmacodynamics." Pharmacodynamics was viewed as a subdividion of pharmacology. As the science of pharmacodynamics evolved into an independent experimental discipline, however, it appropriated to itself the name of "pharmacology." The older, broader meaning of the term eventually became obsolete, and today pharmacology is defined as the study of the interaction of chemical agents with living matter.

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Modern pharmacology is thus a biological science closely akin to physiology, and the purpose of my paper today is to examine the early development of this discipline in the United States.

By way of background, however, I must first briefly discuss the origins of this science in Europe. Experiments on the physiological effects of drugs and poisons upon animals and humans were carried on even in antiquity, but such experiments were generally isolated incidents and not part of a systematic investigation into the action of drugs. Knowledge concerning the therapeutic actions of drugs was largely accumulated empirically from clinical observations.

In the 17th century, under the stimulus given to biological experimentation by William Harvey and others, many investigators experimented on the action of poisons upon animals. In the words of one historian describing the studies, however, "few contributed anything to pharmacology, the majority serving only to confirm that poisons were poisonous." But the 17th and 18th centuries did witness a number of careful and systematic experimental studies on the action of drugs and poisons, which led to the development of useful experimental techniques even if they had no outstanding effect on therapeutics or on the understanding of the physiological action of drugs.

The birth of experimental pharmacology is, however, generally associated with the work of the French physiologist Francois Magendie in the early 19th century. Magendie's researches on strychinine-containing plants clearly established the site of action of these substances as being the spinal cord and provided strong evidence for the view that drugs and poisons must be absorbed into the bloodstream and carried to the site of

action before producing their effects. His careful studies were models of pharmacological experimentation, and his work was extended further by the investigations of his pupil Claude Bernard on curare and carbon monoxide. Bernard was able to establish that curare exerted its paralyzing effect by interferring with the nervous-muscular connection and that the toxicity of carbon monoxide was due to its ability to displace oxygen from its combination with hemoglobin. Thus, in the 19th century, pharmacological researches were beginning to reveal for the first time the physiological mechanisms through which drugs exerted their effects.

The emergence of experimental pharmacology as a science during this period was largely dependent upon advances being made in physiology and chemistry. An understanding of physiological processes was, of course, a necessary prerequisite to an understanding of how drugs altered these processes. Improved chemical techniques led to the isolation of the active ingredients of crude drug substances, such as the plant alkaloids. Pharmacological investigators were thus enabled to work, at least in some cases, with relatively pure chemical substances rather than with complex mixtures containing several constituents with different pharmacological properties. So, for example, the effects of quinine, isolated from cinchona bark in 1820, could be investigated apart from the effects of other constituents present in the bark.

The studies of Magendie, Bernard and other physiologists helped to establish a science of experimental pharmacology. But these men were physiologists and their pharmacological work represented only one aspect of their research. For pharmacology to establish itself as an independent

discipline, related to but distinct from physiology, individuals were required who would devote their full time and efforts to the new science. It was actually in the German-speaking world, rather than in France, that pharmacology was to emerge as a well-defined discipline in the second half of the 19th century.

Rudolf Buchheim, a German by birth, was probably the first person to actively press the case for experimental pharmacology as a separate discipline. Chairs of materia medica had, of course, long existed in medical schools. But materia medica concerned itself largely with questions such as the origin and constituents of drugs, their preparation and traditional therapeutic uses, etc. It was more closely allied to chemistry, botany and pharmacy than it was to physiology. One of the traditional materia medica courses inspired Charles Darwin to comment: "I shall ever hate the name of materia medica since hearing Duncan's (University of Edinburgh) lectures at eight o'clock on a winter morning - a whole, cold breakfastless hour - on the properties of rhubarb." It was a subject that was rather low in the pecking order in medical schools, a handmaiden to therapeutics. The occupant of the chair of materia medica sometimes had to teach a number of other subjects as well. Thus, in 1847, Rudolf Buchheim accepted a chair of materia medica, dietetics, and history and encyclopedia of medicine at the University of Dorpat. While Dorpat was in Russian-governed Estonia, the university was essentially German.

In that same year, 1847, Buchheim established a laboratory for experimental pharmacology in his home, creating probably the first pharmacological institute in the world. Later a pharmacological laboratory was set up for

him in the University. He called for an independent, experimental discipline of pharmacology, arguing that the investigation of the action of drugs is a task for the pharmacologist rather than for the chemist or the pharmacist. As for some of the more traditional aspects of materia medica, Buchheim noted that: "The pharmacologist has as little interest in the appearance of senna leaves as he has in the appearance of the case holding the scapels which he uses for his operations."

A number of students received research training in Buchheim's laboratory, one of whom was Oswald Schmiedeberg, who was undoubtedly more influential than any other individual in helping to make Buchheim's dream of an independent discipline of pharmacology become a reality. In 1866, Schmiedeberg succeeded his teacher Buchheim at Dorpat when the latter moved to Giessen, but it was after he had been appointed to a chair at Strassburg in 1872 that he achieved his greatest success. Schmiedeberg's pharmacological institute at Strassburg became a mecca for students from all over the world. It has been estimated that about 120 students from some 20 different countries worked in his laboratory, and that his students later occupied approximately 40 academic chairs throughout the world. He also founded the first journal of experimental pharmacology.

It was one of Schmiedeberg's students, John J. Abel, who carried back the new science of experimental pharmacology from Germany and established it in America. Pharmacological experiments had, of course, been carried out earlier in the United States, for example, by physicians such as Horatio C. Wood and Silas Weir Mitchell of Philadelphia. Both Mitchell and Wood, however, were probably better known for their neurological studies and their clinical work than for their experimental researches on the action

of drugs. While more research must be devoted to the pioneering efforts of such individuals in order to clarify their role in the development of pharmacology in America, it seems clear that it was Abel and others of his generation who firmly established experimental pharmacology as a distinct discipline in this country.

Materia medica, as taught in American Medical Schools in the late 19th century, generally consisted of the traditional didactic lectures on the botanical origin, constituents, empirical therapeutic uses, dosages, etc. of drugs, and did not involve laboratory work nor experimental demonstrations with animals. It was often taught "by one of the minor members of the faculty who hoped it might be a stepping-stone to something better," and was usually combined with a variety of other teaching duties such as chemistry, botany, medical jurisprudence, clinical medicine, hygiene, etc. Abel's predecessor at the University of Michigan, for example, held the title of Professor of Materia Medica, Ophthamology, Aural Surgery and Clinical Ophthamology.

When this chair became vacant in 1889, the University of Michigan Medical School, at the urging of Victor Vaughan, then Professor of Physiological and Pathological Chemistry and later Dean of the Medical School, decided to use this opportunity to create a chair of modern pharmacology. Vaughan was in touch with the rapid advances being made in the medical sciences and had spent his vacation in 1888 in Robert Koch's laboratory in Berlin learning the techniques and concepts of the new science of bacteriology. Abel had received his undergraduate training at the University of Michigan, where he had spent some time working in Vaughan's laboratory. After further study at Johns Hopkins, he then made the pilgrimage to Europe so customary

for ambitious young American scientists in the late 19th century. Abel's European apprenticeship is one of the longest on record, as he spent about six and one-half years working in various laboratories in Germany and Switzerland, including two years at Strassburg where he received his MD degree in 1888. Here he came into contact with the pharmacologist Oswald Schmiedeberg and worked in his laboratory.

Abel had been preparing himself for a career in physiological chemistry, another newly emerging discipline. He wrote to Vaughan concerning job prospects in the United States at the time that the latter was beginning to search for a pharmacologist to fill the vacant chair of materia medica at Michigan. Vaughan's former acquaintance with Abel, their common interest in physiological chemistry, and recommendations from Schmiedeberg and others, prompted Vaughan to recommend Abel for the position. Abel, recognizing that he could apply his biochemical training to pharmacology, a subject which had attracted his attention in Schmiedeberg's laboratory, decided to accept the offer. He wrote home to his wife, then in the United States, that chemistry was as necessary in pharmacology or therapeutics as it was in physiological chemistry and he added: "I know that I can make vastly more out of pharmacology in the States." So, in 1891, Abel took up his duties in Ann Arbor. Because of his interest in chemistry and his conviction of its value for medicine, most of his pharmacological researches had a biochemical bent, and he also played a significant role in the establishment of biochemistry as a discipline in America.

Abel brought with him to Michigan the German tradition of experimental pharmacology as molded by Buchheim and Schmiedeberg. He soon set up a research laboratory, converted the course on materia medica into a

pharmacology course which included laboratory work and experimental demonstrations, and develped advanced laboratory courses on the methods of modern pharmacology and on the influence of drugs on tissue metabolism.

In a lecture given to the Michigan State Pharmaceutical Association in 1891, Abel expounded his view of the new discipline of pharmacology.

"Briefly, this science tries to discover all the chemical and physical changes that go on in a living thing that has absorbed a substance capable of producing such changes, and it also attempts to discover the fate of the substance incorporated. It is not therefore an applied science, like therapeutics, but it is one of the biological sciences, using that word in its widest sense . . . Its growth is intimately connected with that of physiology."

He noted that Buchheim and others had developed pharmacological laboratories where experimenters could build up their science "undisturbed by the instrusive demands of practical utility" (i.e., the demands of therapeutics). He was quick to point out, however, that once pharmacology was placed on a firm basis it would automatically yield results of value to the practical man.

As for the more traditional aspects of materia medica, Abel later noted that when he began teaching pharmacology he discarded all separate instruction in materia medica. Ih his course lectures on drugs such as digitalis, ergot, opium, etc., he made a few brief historical remarks about these substances, as well as giving a short account of their chemical composition and behavior toward solvents, then rapidly proceeded to a discussion of their pharmacological actions. But he did not think it wise

"to overburden the student's mind with a multitude of dry details of interest or value solely to the pharmacist or the student of pharmacognosy."

About the time that Abel went to Michigan, the Johns Hopkins University was making preparations for the establishment of its medical school on the Germanic model. A faculty of exceptionally high quality was being assembled, and Hopkins was soon to become the finest medical school in the country. In January of 1893, William Osler wrote to Abel to ask "On what terms could you be dislocated?" He indicated that he felt that no one in America had a better training in pharmacology than Abel, and that Hopkins would be pleased to have him on their faculty. That same year, Abel became Professor of Pharmacology at Hopkins, occupying what was apparently the first chair in the United States with that title (since Michigan had retained the old designation of materia medica and therapeutics). Abel spent the rest of his career at Johns Hopkins, training a host of future American pharmacologists and carrying out important researches such as those leading to the isolation of epinephrine in the form of its benzoyl derivative and those leading to the crystallization of insulin. In a sense, Abel's laboratory played a similar role to that of Schmiedeberg earlier, but not on the same international scale. A whole generation of American pharmacologists was trained in his laboratory (although, of course, others, including his own students, began to build up programs of their own). His laboratory played a crucial role in the early development of American pharmacology in providing trained pharmacologists for the posts opening up.

Meanwhile, a number of other American medical schools were beginning

to make the transition from materia medica to pharmacology. At Michigan, the pharmacological department had continued on after Abel's departure under the direction of the Scot Arthur Cushny, who had also studied in Schmiedeberg's laboratory. In 1899, he published what can probably safely be regarded as the first textbook of modern pharmacology in the English language. In 1894, Western Reserve University appointed a young physician who had received pharmacological training as an assistant to Schmeideberg to teach pharmacology. Although he did not remain in the position long, the faculty agreed to replace him with Torald Sollmann, then an assistant in physiology, after sending Sollmann to study with Schmiedeberg for a semester. Still another Schmiedeberg trained scientist, Franz Pfaff, became professor of pharmacology at Harvard around the turn of the century (when the title of the chair was changed from materia medica). A number of other pharmacology programs were established in American medical schools in the first decade of the 20th century but I will not burden you with the details here. Let me just mention, as examples, that I think we can date the beginnings of programs in modern pharmacology at Columbia, Cornell, Virginia, Tulane and Wisconsin, among others, in this period.

The transition from materia medica to pharmacology, I might just note, took place at a much later date at most American schools of pharmacy. The history of the teaching of pharmacology in American schools of pharmacy and its relationship to views about the role of the pharmacist is an interesting subject, but one that is beyond the scope of the present paper.

The new science of pharmacology also began to find a place in government and other institutional research laboratories in the early 20th century. The Hygienic Laboratory of the United States Public Health

Service (precursor of the National Institutes of Health), for example, established a Division of Pharmacology with Reid Hunt, a student of Abel, as its first chief in 1904. Hunt later went on, in 1914, to become head of the Pharmacology Department at Harvard. The United States Department of Agriculture began employing research pharmacologists in divisions such as the Bureau of Chemistry and the Bureau of Plant Industry. During this same period, the newly founded Rockefeller Institute established a Department of Physiology and Pharmacology as one of its divisions.

The American Pharmaceutical Industry was also beginning to recognize the value of systematic research in the development of drug products around the turn of the 20th century, and modern pharmacology was a science which was relevant to the needs of the drug industry. The need to develop standardized products had led to the establishment of certain quality control procedures by the more progressive firms, and this necessitated the hiring of chemists to do the analytical work. The passage of the Federal Food and Drug Act of 1906 further stimulated the development of quality control in the drug industry. The early research activities of American pharmaceutical firms often emerged out of this concern over quality control and drug standardization.

When diptheria antitoxin was introduced into medical practice in the early 1890's, Parke, David and Company was one of the first American firms that decided to embark upon the manufacture of the antitoxin. They consulted the University of Michigan Medical School in 1894 concerning the setting up of a bacteriological laboratory, and obtained the services of Charles McClintock and Elijah Houghton, two young assistants in the medical school at that time. McClintock's interests seem to have been in bacteriology

and physiological chemistry. Houghton, who had received his M.D. at Michigan in 1894, was an Assistant Instructor in Pharmacology under Arthur Cushny (the man who had succeeded Abel).

While McClintock and Houghton were brought in to Parke, Davis to organize the production of diptheria antitoxin, they were also given a free hand to pursue research. By 1896, McClintock had formally been designated as Director of Research with Houghton as Assistant Director. Houghton's research largely centered around the development of physiological or biological standardization procedures for drugs (i.e., techniques for standardizing drugs based upon the quantitative measurement of some pharmacological response). He appears to have been the first industrial scientist in the United States whom we can designate as an experimental pharmacologist, and he eventually became the director of Parke Davis' medical research program.

As other drug companies began to involve themselves in research, they also eventually hired pharmacologists as important members of their research teams. The Eli Lilly Company, for example, had individuals identified as pharmacologists as part of its scientific staff by 1912 at the latest, and probably earlier. It is interesting to note that when the American Society for Pharmacology and Experimental Therapeutics, which is discussed below, was founded in 1908, there was a specific provision in the by-laws that no pharmacologist in the full-time employ of a drug firm could become a member. While there were very few pharmacologists in industry at that time, Abel and others apparently felt that this group might eventually come to dominate the Society, and apparently they mistrusted them. This provision was not changed until 1941.

As the first decade of the twentieth century drew to a close, American pharmacology had progressed in its search for a separate identity to the point where its practitioners felt the need for a separate organization of pharmacologists. As early as 1907 Abel had begun to communicate with other pharmacologists about the possibility of establishing a national society. In early 1908, he wrote to Sollman: "It is high time that we started a society. Our subject is suddenly getting popular. Twenty years ago there was very little interest taken in it."

Abel went on to say that the medical schools were finally waking up to the need for the subject, and that during the last year there were ten openings for pharmacologists in universities and not enough good men to fill them. A society of pharmacologists, Abel felt, would give young men in the field an opportunity to present research papers and discuss their results and views with their colleagues. He also felt that there was a need for a journal in the field, and indicated that he was working on that problem as well.

On December 28, 1908, when the American Physiological Society and the American Society of Biological Chemists meeting in Baltimore, 18 men interested in pharmacology met at Abel's invitation in his laboratory at Johns Hopkins to organize the new society, to which they gave the name "American Society for Pharmacology and Experimental Therapeutics." The latter portion of the title was apparently added to emphasize the close relationship of pharmacology to the newly emerging field of chemotherapy, which had just been opened up by the work of Paul Ehrlich. Abel was elected as the first president of the organization, while his former students

Reid Hunt and Arthur Loevenhart became secretary and treasurer respectively.

At the organizational meeting, Abel announced that he was establishing The Journal of Pharmacology and Experimental Therapeutics and invited the members of the new society to be collaborators in this project. Although the Journal did not become the official organ of the Society until 1933, when the Society took over its ownership from Abel, its relationship to the Society was a close one from the very beginning. Abel served as editor of the publication from its founding in 1909 until his retirement from his university post in 1932. By the end of the first decade of the 20th century American pharmacologists thus had their own national society and their own specialized medium for the publication of research results, signs that pharmacology was achieving status as an independent scientific discipline in the United States. Of course, the number of pharmacologists in America was still relatively small in 1910, and many more years were to pass before the discipline was firmly established in the medical curricula of all universities, in the research laboratories of all of the major pharmaceutical firms, etc. Time does not permit me, however, to trace the entire development of pharmacology in this country. I have instead focused my attention on the crucial period when the science was first establishing itself as an independent discipline.

I have, of course, only been able to present a sketchy narrative overview of the early history of pharmacology in America. Aside from any question of time limitations, there is also the problem that the history of the subject in a real sense has yet to be written. What I have presented to you today is a preliminary report on a research project on which I have only made a very limited beginning and I realize that I have raised more questions than I have answered. It is my intention, over the next few

years, to examine the early development of pharmacology in the United States in detail and to flesh out the skeleton which I have exhibited to you today, hopefully providing an understanding of how and why the subject developed as it did.